

Clinical equivalence of a novel non-chlorofluorocarbon-containing salbutamol sulfate metered-dose inhaler and a conventional chlorofluorocarbon inhaler in patients with asthma

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Background: New formulations of non-chlorofluorocarbon-containing propellants for pressurized metered-dose inhaler delivery systems must be developed in response to the forthcoming ban on chlorofluorocarbon (CFC) production.

Objective: This study compared the bronchodilator effects of 100, 200, and 300 µg (base equivalent) of salbutamol in a novel CFC-free propellant system (Airomir in the 3M CFC-Free System; 3M Pharmaceuticals, St. Paul, Minn.; 108 µg of salbutamol sulfate or 90 µg of salbutamol base equivalent per inhalation) with that of 100 and 200 µg of salbutamol base in a conventional CFC propellant system (Ventolin, CFC-11/12; Allen and Hanburys, Division of Glaxo Inc., Research Triangle Park, N.C.; 90 µg of salbutamol base per inhalation) and placebo.

Methods: Twenty-six patients with chronic, stable asthma, who had a forced expiratory volume in 1 second (FEV₁) between 50.0% and 75.0% of predicted normal value, entered this randomized, double-blind, double-dummy, 6-period, crossover study. FEV₁ was measured before and at multiple time points (ranging from 10 to 480 minutes) after administration of one, two, and three inhalations of salbutamol/CFC-free (100, 200, and 300 µg); one and two inhalations of salbutamol/CFC (100 and 200 µg); and placebo. Safety parameters included adverse events, heart rate, blood pressure, physical examinations, electrocardiograms, and clinical laboratory tests. Parametric analysis of variance models appropriate for a 6-period crossover design were used, along with multiple comparisons according to Tukey's method.

Results: All active treatments produced significantly ($p < 0.0001$) greater bronchodilation than placebo. The bronchodilator effect, as measured by FEV₁ (peak percent change, peak as a percent of predicted value, duration, and area under the curve) after two inhalations of salbutamol/CFC-free was clinically comparable to two inhalations of salbutamol/CFC, with no clinically meaningful differences in safety parameters between the two delivery systems or between different dose levels.

Conclusion: These results suggest that salbutamol/CFC-free may offer a suitable alternative for salbutamol/CFC when the need arises to change from CFC-containing salbutamol products. (*J ALLERGY CLIN IMMUNOL* 1995;96:50-6.)

Key words: Salbutamol, asthma, hydrofluoroalkane, HFA-134a, bronchodilator

Chlorofluorocarbons (CFCs) are an essential component of current pressurized metered-dose inhalers (MDIs), which deliver drugs for the treat-

ment of reversible obstructive airway disease (asthma). During the 1970s, scientists suggested that the growing nonmedicinal use of CFCs was reducing the concentration of the stratospheric ozone layer

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Abbreviations used

ANOVA:	Analysis of variance
CFC:	Chlorofluorocarbon
FEV ₁ :	Forced expiratory volume in 1 second
HFA:	Hydrofluoroalkane
MDI:	Metered-dose inhaler

with potentially harmful results. Under the auspices of the United Nations Environmental Program, a committee designated to study the effects of CFCs on the ozone layer organized the preparation of a CFC protocol. Ratified by over 100 nations, the Montreal Protocol will lead to the reduction in and eventual cessation of CFC production by January 1, 1996.

Although other delivery systems (e.g., nebulizers and dry powder inhalers) do not use CFCs, MDIs are widely used and accepted and are the preferred method of treatment for many patients. The reformulation of MDI propellants from CFC-containing to CFC-free systems could have an impact on an estimated 250 million patients worldwide. One aim of reformulation would be to ensure continued availability of MDIs as a method of treatment while using a safe and effective system that addresses environmental concerns.

A hydrofluoroalkane (HFA), designated propellant 134a (CF₃CH₂F), is considered to be one of the two present alternatives to CFC propellants. Like the CFCs, HFA-134a is chemically inert.^{1,2} Unlike the CFCs, HFA-134a (tetrafluoroethane) has no chlorine and therefore no ozone-depleting potential.

The preclinical toxicologic testing program of HFA-134a has been reviewed by the Committee for Proprietary Medicinal Products (CPMP, the European Regulatory Agency). The Committee stated that there were no significant pharmacologic, toxicologic, or safety issues found during their reviews.³ For further information about HFA-134a, the reader is referred to Leach (1995) and Boulden (1994).^{1,2}

In this study salbutamol sulfate (albuterol), a selective β_2 -adrenergic agonist currently available for inhalation asthma therapy, has been reformulated with the new HFA-134a propellant system. Because this formulation change incorporates HFA-134a, which is not yet licensed as an excipient for use in medicinal products, clinical trials to provide safety and efficacy data are required by relevant regulatory agencies worldwide.

The objective of this study was to determine the

dose of salbutamol sulfate in an HFA-134a propellant system (Airomir in the 3M CFC-Free System, 3M Pharmaceuticals, St. Paul, Minn.), referred to as salbutamol/CFC-free 108 μ g of salbutamol sulfate or 90 μ g of salbutamol base equivalent per inhalation that produced clinical efficacy comparable with two inhalations of salbutamol base in a conventional CFC-11/12 propellant system (Ventolin, CFC-11/12, Allen and Hanburys, Division of Glaxo, Inc., Research Triangle Park, N.C.) referred to as salbutamol/CFC 90 μ g of salbutamol base per inhalation, in patients with asthma. A placebo treatment was included as a reference. The primary objective measure was efficacy as assessed by forced expiratory volume in 1 second (FEV₁). The safety parameters of the study were sitting heart rate and blood pressure, electrocardiograms, adverse events, physical examinations, and clinical laboratory tests.

METHODS

Study design

This study was designed as a randomized, single-dose, double-blind, double-dummy, 6-period crossover trial of salbutamol/CFC-free, salbutamol/CFC, and placebo (a combination treatment of CFC and CFC/free systems) in 26 nonsmoking patients with stable bronchial asthma. A sample size of at least 24 subjects was necessary to provide at least 80% power to detect at $\alpha = 0.05$ the differences between each of the active treatments and placebo. Patients had to demonstrate prestudy screening baseline FEV₁ values between 50.0% and 75.0% of the predicted normal value after washout of bronchodilator drugs and an increase in FEV₁ of at least 20% within 30 minutes after an inhalation of 200 μ g of salbutamol/CFC. Patients were randomized to groups of six so that a total of four patients was randomly assigned to each of the six possible sequences. Patients received a total of four inhalations at each of the six dosing periods with a 1-day washout between each period. To blind the study treatment and the dose level, patients received a companion placebo with each dose of study medication; they received a corresponding number of inhalations of the placebo to equal a four-inhalation dose (Table I).

Clinical methods

Before study initiation, the protocol was reviewed and approved by an institutional review board. Each patient voluntarily signed a written informed consent form. The study was conducted according to good clinical practice standards.

Patients entered the clinical unit on the evening before study period 1 and remained there for the duration of the study. Use of asthma medications, with the exception of inhaled β -agonists, was prohibited during the study. Inhaled β -agonists were withheld for 8 hours before pulmonary function tests were performed

TABLE I. Treatment combinations

1 puff Salbutamol/CFC-free	+	3 puffs CFC placebo
2 puffs Salbutamol/CFC-free	+	2 puffs CFC placebo
3 puffs Salbutamol/CFC-free	+	1 puff CFC placebo
1 puff Salbutamol/CFC	+	3 puffs CFC-free placebo
2 puffs Salbutamol/CFC	+	2 puffs CFC-free placebo
3 puffs CFC-free placebo	+	1 puff CFC placebo

at screening and each of the six study periods. Allergy medications were permitted. Patients continued to take their prescribed inhaled β -agonists for the duration of the study, except for an 8-hour washout period before and during the testing period in each of the six study periods. None of the patients received inhaled steroids or cromolyn during the trial. Caffeine-containing beverages were withheld.

Within 30 minutes before dosing in each of the six study periods, the baseline FEV₁ was required to be within $\pm 15.0\%$ of the screening FEV₁ and could not exceed 85% of predicted normal FEV₁. Patients who did not meet these criteria were allowed additional attempts, provided that they were able to complete the study within 16 days. Baseline measurements of blood pressure, heart rate, and electrocardiogram were taken, and a physical examination and laboratory tests were completed.

Doses were administered between 7:00 and 9:00 AM and within 1 hour of the time of dosing in study period 1 for each of the consecutive study periods. Patients dosed themselves under the supervision of a study nurse. Patients inhaled a total of 4 puffs from two inhalers according to the randomization sequence. All inhalations per dose level were administered approximately 45 seconds apart (from the start of one inhalation to the start of the next). Time 0 was the time when the MDI was first actuated (i.e., the time of the first puff of the dose).

Pulmonary function tests were performed at 10, 15, 30, 45, 60, 90, 120, 180, 240, 300, 360, 420, and 480 minutes from time 0 of the dose administration. All pulmonary function tests were performed at least three times in a standing position, in compliance with the American Thoracic Society statement on standardization of spirometry,⁴ with a Puritan Bennett Processing (PS600) spirometer (Puritan-Bennett Corp., Overland Park, Kan.), which recorded and printed time volume curves. Patients were instructed to produce a maximal forced expiration over at least 6 seconds. Triplicate measurements of FEV₁ were made with a 1-minute interval between each determination. The values recorded for FEV₁ were from the best individual test. If

TABLE II. Prestudy screening data for 26 patients entering the study

Response	Value
Predicted FEV ₁ (L)	
Mean (SD)	4.07 (0.59)
Range	2.32-4.68
Screening FEV ₁ (L)	
Mean (SD)	2.64 (0.44)
Range	1.58-3.36
Screening FEV ₁ as a percent of predicted value	
Mean (SD)	65.2 (6.9)
Range	51.4-74.1
Postreversibility FEV ₁ (L)	
Mean (SD)	3.47 (0.57)
Range	2.32-4.70
Percent FEV ₁ reversibility	
Mean (SD)	32.0 (13.3)
Range	20.1-76.9

these tests did not meet acceptability criteria, more tests were performed until acceptability criteria were met.

Pulmonary function testing was stopped and rescue medication was given if a patient had a fall in FEV₁ of 15% or greater from baseline measured in that study period and an accompanying increase in symptoms, a fall in FEV₁ below 40.0% of predicted FEV₁, or at the investigator's discretion if the patient was in distress.

Statistical methods

For the FEV₁ data, the following parameters were calculated for each patient and treatment.

1. Responders. A patient was considered a responder at a visit if his or her FEV₁ increased at least 15.0% over baseline within 30 minutes after study treatment administration.
2. Peak response as a percentage increase over baseline and as a percentage of the predicted value. Also, the peak change as a percentage of the maximum possible change was determined:

$$\frac{\text{Peak FEV}_1 - \text{Baseline FEV}_1}{\text{Predicted FEV}_1 - \text{Baseline FEV}_1} \times 100\%$$

3. Time of onset of effect. The onset of effect was determined by linear interpolation of the time that FEV₁ first exceeded 15.0% over baseline within 30 minutes after study treatment administration.
4. Duration of effect. The therapeutic response was considered to have ended when the FEV₁ fell below 15.0% over baseline for two consecutive measurements. The time of termination of effect was estimated by linear interpolation between the last measurement greater than 15.0% over baseline and the first of the two consecutive measurements less than

TABLE III. Results for responses based on FEV₁ for 25 patients in each treatment group compared with placebo

Response	Placebo	Salbutamol/CFC-free			Salbutamol/CFC		p Value*
		1 Puff	2 Puffs	3 Puffs	1 Puff	2 Puffs	
AUC (% hr)							
Mean	23.4	74.4	117.0†	125.0†	98.1†	115.6†	0.0001
SD	74.9	89.9	136.5	141.7	114.9	118.4	
Peak % change							
Mean	15.5	26.8†	31.1†	31.6†	29.1†	31.2†	0.0001
SD	14.5	18.7	24.0	19.0	20.0	22.1	
Peak change (L)							
Mean	0.43	0.70†	0.81†	0.85†	0.77†	0.80†	0.0001
SD	0.38	0.34	0.49	0.47	0.46	0.43	
Peak as % of predicted value							
Mean	78.9	85.7†	89.4†	89.6†	88.0†	88.2†	0.0001
SD	11.5	11.4	12.8	12.2	11.1	11.2	
Peak change as % of max change							
Mean	35.1	58.9†	67.2†	70.4†	63.0†	65.3†	0.0001
SD	26.4	32.8	38.7	40.4	41.0	38.0	
Duration of effect (hr)							
Mean	0.8	2.8†	3.8†	4.0†	3.2†	3.6†	0.0001
SD	2.2	3.0	3.4	3.0	3.3	3.4	
responders							
No.	5	16†	17†	20†	17†	17†	0.0001
%	20%	64%	68%	80%	68%	68%	
Time of onset of effect (min)‡							
Number	5	16	17	20	17	17	0.039
Mean	11	6†	5†	6†	6†	5†	
SD	6	3	2	3	4	3	

Results are based on data from the 25 patients who completed all six periods.

AUC, Area under the curve.

*The p value tests the effect of treatment from an ANOVA for a 6-period crossover.

†The mean was significantly different from that of placebo as determined by ANOVA with Tukey's method of multiple comparisons.

‡The time of onset was only defined for patients who responded to the assigned treatment.

15.0% over baseline. The duration of effect was defined as time of termination of effect minus time of onset of effect. For patients who did not respond at a visit, the duration of effect was defined to be zero for that visit.

5. Area under the curve. The area-under-the-curve measurements were calculated with the percentage change from baseline FEV₁ data, from onset of effect to termination of effect.

Responses based on FEV₁ were tested by an analysis of variance (ANOVA) with sequence, patient within sequence, treatment group, and period as factors in the model. The test of sequence effect was determined with the patient within sequence mean square as the error term in the denominator. A p value of less than 0.05 was considered significant. If the treatment effect was considered significant, multiple comparisons were done with Tukey's method.

The statistical software used to analyze the data was PROC GLM from SAS Version 6.07 (SAS Institute, Cary, N.C.).⁵

RESULTS

Study population

Twenty-six patients (20 men and 6 women) with asthma history of at least 1 year participated in at least one treatment period. Of these, 25 completed all six treatment periods of the study. One patient was withdrawn from the study after one treatment period because of inability to meet the baseline variability criterion. Mean age was 28 ± 9 years (range, 18 to 50 years). Mean height was 178 ± 4 cm, and mean weight was 81 ± 16 kg. Eighteen patients (69%) also had allergies.

FEV₁

Table II lists mean prestudy spirometry screening data. Before dosing in each of the study periods, the mean baseline FEV₁ was 2.80 L or 68.7% of predicted value. There were no significant differences in FEV₁ before subjects entered

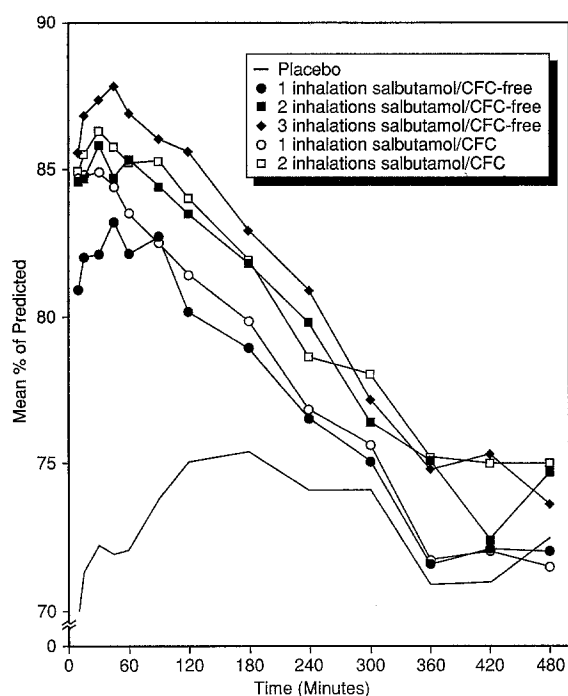


FIG. 1. Mean FEV₁ as a percentage of predicted value over time in 25 patients.

the first period. As determined by ANOVA, there were no significant differences in baseline FEV₁ values between the six treatment groups.

A comparison of the mean FEV₁ data for each of the six treatment groups indicated that the effect of two inhalations of salbutamol/CFC-free most closely matched the effect of two inhalations of salbutamol/CFC (Table III). There were no significant differences between any of the active formulations for any of the FEV₁ responses. On the basis of peak percentage change, peak change, peak change as percentage of predicted value, peak change as percentage of maximum possible change, duration of effect, and time of onset, the results for all five active treatment groups (1, 2, and 3 puffs of salbutamol/CFC-free and 1 and 2 puffs of salbutamol/CFC) were significantly greater than that of placebo. For area under the curve, the results of all active treatment groups, with the exception of one inhalation of salbutamol sulfate, were significantly greater than placebo. Although a dose-response trend was seen for both salbutamol/CFC-free and salbutamol/CFC, there were no statistically significant differences between any of the five active treatments for any of the responses.

The data were also analyzed after each patient's change in FEV₁ was converted into a percentage change in FEV₁ relative to the patient's predicted

normal FEV₁ (with the normal prediction equation of Morris et al.).⁶ Mean FEV₁ values as a percentage of predicted FEV₁ over time are presented in Fig. 1. The effects of all five active treatments were significantly greater than the effect of placebo throughout the first 90 minutes. For two and three inhalations of salbutamol/CFC-free, the results were significant throughout the first 240 minutes. Results of one and two inhalations of salbutamol/CFC were significant throughout the first 120 and 180 minutes, respectively. For this comparison, two inhalations of salbutamol/CFC-free most closely matched two inhalations of salbutamol/CFC.

Rescue bronchodilator use

Pulmonary function testing was discontinued before completion of the 8-hour testing period for four patients on eight separate occasions (Table IV). No patient experienced any acute respiratory problems requiring rescue treatment within 60 minutes after administration of any of the six treatments, and no patient receiving salbutamol/CFC-free required rescue treatment sooner than 300 minutes after dosing. All patients returned to baseline pulmonary function after receiving standard bronchodilator treatment.

Safety

Before dosing on each of the study days, the mean baseline pulse was 76 beats/min, and the mean baseline blood pressure was 115/70 mm Hg. As determined by ANOVA, there were no significant differences in baseline vital signs among the six treatment groups.

For change from baseline pulse, according to ANOVA, the only significant treatment effect occurred at 300 minutes ($p = 0.024$). Because 13 tests of significance were done with these data, this was believed to be due to chance alone. There were no significant sequence or period effects. For change from baseline systolic and diastolic blood pressure, according to ANOVA, there were no significant differences among the six treatment groups, and there were no significant sequence or period effects. Comparison of prestudy and poststudy 12-lead electrocardiograms, results of physical examinations, and laboratory values revealed no clinically significant findings.

A total of 19 adverse events were reported by 12 patients during the course of the study. All of these were mild or moderate in intensity, none of them resulted in patient withdrawal, and all were resolved by the end of the study. The most commonly reported adverse event was headache. A full listing

TABLE IV. Rescue bronchodilator administration

Treatment group	Patient No.	Dose (puffs)	Last PFT time (min)	Reason
Placebo	13	—	420	FEV ₁ dropped below 40% of predicted value
	23	—	240	FEV ₁ dropped $\geq 15\%$ from baseline/asthma symptoms
	122	—	60	Investigator's discretion
Salbutamol/CFC	8	1	240	FEV ₁ dropped $\geq 15\%$ from baseline/asthma symptoms
	23	2	420	FEV ₁ dropped $\geq 15\%$ from baseline/asthma symptoms
	122	1	360	FEV ₁ dropped below 40% of predicted
Salbutamol/CFC-free	13	3	300	FEV ₁ dropped below 40% of predicted
	122	2	360	Investigator's discretion

TABLE V. Adverse events by treatment group

Adverse event	Placebo (n = 25)	Salbutamol/CFC-free			Salbutamol/CFC	
		1 puff (n = 25)	2 puffs (n = 25)	3 puffs (n = 26)	1 puff (n = 25)	2 puffs (n = 25)
Headache	1	1	1	2*	1*	3*
Rhinitis†	1	1	1	1	1	1
Chest pain	1			1		1
Dyspepsia		1‡	1	1‡		
Dizziness			1		1	
Nausea			1			
Coughing					1	
Abdominal pain		1				
No. of subjects reporting adverse events	3	4	3	5	4	5

*Subject 24 experienced a headache, which remained for three study periods.

†Subject 6 experienced rhinitis, which was present before the study and remained unchanged throughout all periods.

‡Subject 10 experienced dyspepsia, which was present for two study periods.

of the number of subjects reporting an adverse event by treatment group is presented in Table V. It should be noted that because of the crossover design of the study, the total tally of adverse events does not match the data in Table V. This is because subjects 6, 10, and 24 each had one event that lasted for more than one treatment period.

DISCUSSION

This study determined that the reformulation of salbutamol in this CFC-free propellant system produced comparable bronchodilator effects at a dose equivalent to the leading currently marketed CFC-containing salbutamol product. The mean responses, based on FEV₁ data for all six treatment groups, indicated that the effect of two inhalations of salbutamol/CFC-free most closely matched the effect of two inhalations of salbutamol/CFC. This study examined FEV₁ response over time, up to 8 hours after dosing, and demonstrated comparable efficacy of two inhalations of

the two products. All five treatments were significantly more effective than placebo, and although not statistically significant, a dose-response trend was evident for both the CFC-free and CFC-containing products. These patients were taking only inhaled β -agonists for treatment of their symptoms; therefore, no concurrent asthma therapy confounded the results.

This is the first reported study of this salbutamol/CFC-free formulation in patients with asthma. Two previous studies (manuscripts in preparation) of healthy volunteer subjects demonstrated no significant differences in tolerability or safety between the CFC-free and CFC-containing propellant systems. In one study, patients were administered cumulative increasing doses of up to 16 inhalations of the CFC-free formulation compared with the CFC-containing system. In the second study, a long-term safety evaluation, subjects received 16 inhalations per day for 2 weeks, followed by 32 inhalations per day for 2 weeks.

The safety data presented here (i.e., adverse events, vital signs, electrocardiograms, clinical laboratory tests, and physical examinations) indicate that there were no clinically meaningful differences between salbutamol/CFC-free and salbutamol/CFC and also no differences between the studied dose levels of each of the two products. On the basis of the safety data collected, the active and placebo treatments were well tolerated, and there were no safety concerns with the administration of the six study treatments. Further, there was no evidence of bronchoconstrictive effects immediately after placebo administration.

In this study the new product has been assessed for its ability to produce bronchodilation equivalent to the presently marketed product. As pointed out by Wong and Hargreave,⁷ β_2 -adrenergic agonists also manifest a bronchoprotective effect against nonsensitizing agents, such as methacholine or histamine, and against exercise. They suggest clinical equivalence with both responses should be sought until evidence supports the use of one or the other response or until the responses are equivalent. Comparative challenge studies

evaluating the bronchoprotective effect of salbutamol/CFC-free are in progress.

The results to date suggest that salbutamol/CFC-free will offer a suitable alternative for salbutamol/CFC when the need arises to change from CFC-containing salbutamol products.

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